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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,722	09/18/2003	Lee Martin Greenberger	AM101032	9014

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EXAMINER	
JEAN-LOUIS, SAMIRA JM	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
03/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,722	GREENBERGER ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-81* is/are pending in the application.

4a) Of the above claim(s) *8,58,67,69-72 and 80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-57, 59-66, 68, 73-79, and 81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner for this current application at the USPTO has been changed.

Examiner Jean-Louis can be reached at 571-270-3503.

Response to Arguments

Applicant's arguments regarding the requirement for a second restriction requirement has been fully considered. Given that a species requirement was indeed requested of Applicant in the Election/Restriction requirement in the Office Action dated 11/24/06 and Applicant did not provide such species requirement for claims 77, 79, and 81, the second election requirement was indeed proper. Moreover, due to the presence of compounds containing cyclic and saturated and unsaturated linear functional groups, the Examiner asserts that a search would indeed be unduly extensive and burdensome as these species possess contrasting physical and chemical properties and a search for these species would consist of searching multiple databases for various references and literature searches. Thus, the second election/restriction requirement is deemed proper and is therefore made FINAL.

Claims 8, 58, 67, 69-72, and 80 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group and species, there being no allowable generic or linking claim. Claims 1-7, 9-57, 59-66, 68, 73-79, and 81 are examined on the merits herein.

The Examiner further acknowledges applicant's election of paclitaxel as the chemotherapeutic agent to which tumors are resistant; ovarian tumors as the disease to be treated in the method claims; administration of compounds of formula II after

treatment of chemotherapeutic agent and election of example 57 or N,O,ß, ß,-tetramethyl-L-tyrosyl-N'-[(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-N',3-dimethyl-L-valinamide as the compound of formula II to be used in the method recited in claim 1. Moreover, the elected species appears to be free of the art, the search was thus extended to non-elected species of formula II.

The Examiner further acknowledges receipt of the Affidavit dated April 11, 20008. Consequently, the Examiner asserts that the compound of example 57 is enabled. As for applicant's arguments that example 129 provides a roadmap as to how one skilled in the art can readily make and use the compounds of formula II, such arguments are found persuasive. Moreover, applicant argues that *in vivo* data or clinical data is not required under the law or USPTO guidance, again such arguments are found persuasive as the compound of example 129 along with the compound of example 57 which fall under the core structure of formula II were indeed tested (as demonstrated by the affidavit and the specification) and found to be effective in the treatment of tumors and in preventing cell proliferation as demonstrated in the *in vitro* and *in vivo* data. Thus, the rejection of record in the Non-Final Office Action dated December 14, 2007 is hereby withdrawn.

The following objection, modified 112, first paragraph, and 103(a) Non-Final rejections are being made.

Objections

Claim 25 is objected to because of the following informalities: "H" is missing on the carbon containing the isopropyl functional group. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-57, 59-66, 68, 73-79, and 81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds of formula II such as example 57 and 129 in the treatment of certain cancers such as breast, colon, melanoma, etc.., does not reasonably provide enablement for all compounds of formula II in the treatment of every single cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of treating, inhibiting growth of, or eradicating a tumor in a mammal in need thereof wherein said tumor is resistant to at least one chemotherapeutic agent which method comprises providing to said mammal an effective of a compound of formula II or pharmaceutically acceptable salts thereof

with certain provisos. The instant specification fails to provide information that would allow the skilled artisan to practice the treatment of all diseases associated with immunoregulatory abnormality.

In re Sichert, 196 USPQ 209 (CCPA 1977)

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to a method of treating, inhibiting growth of, or eradicating a tumor in a mammal in need thereof wherein said tumor is resistant to at least one chemotherapeutic agent which method comprises providing to said mammal an effective of a compound of formula II or pharmaceutically acceptable salts thereof with certain provisos. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. Particularly, the examiner cites the fact that cancer is a complex disease wherein each cancer possesses contrasting pathophysiology and contrasting etiology thereby rendering it impossible for one compound to treat every single cancer or tumors. Moreover, applicant claims treatment of all tumors regardless of the tumor origin with every single compound that falls within the scope of formula II, yet applicant's own limited *in vitro* data in the specification demonstrate that certain compounds such as compounds 157,

123, 45, 88, or 1a were not effective in inducing death in the paclitaxel-resistant cell lines. These results thus raise serious doubt to one skilled in the art as to whether all of the compounds of formula II are indeed effective in the treatment of cancer.

2. The breadth of the claims

The claims are thus very broad insofar as they recite the "treatment of all tumors" using every single compound that falls within the scope of formula II. While such "treatment" might theoretically be possible *in vitro,* as a practical matter it is nearly impossible to achieve a treatment for all cancers with the same compound.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for the treatment of mouth, pancreatic or kidney tumors, for example, with the compounds of formula II; yet applicant claims the treatment of such cancers. No reasonably specific guidance is provided concerning treatment of every single cancer with the aforementioned compounds, other than melanoma, colon, breast, and epidermoid tumors. The latter is corroborated by the working examples in tables 1-12.

The instant disclosure provides no evidence to suggest that this unique activity can be extrapolated to brain cancer, for example, having unrelated mechanisms of resistance, and thus does not meet the "how to use" prong of 35 USC 112, first paragraph with regard thereto.

Additionally, applicant failed to provide enablement for the treatment of the elected

cancer species, ovarian tumors. Moreover, the claims recite the use of numerous compounds of formula II having contrasting structures and yet fail to provide enablement for such compounds especially given that some compounds were not quite effective in the reducing the growth of resistant tumors.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed compounds could be predictably used for the treatments of all cancers/tumors as inferred by the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

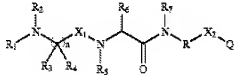
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 9-57, 59-66, and 68 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Kowalczyk et al. (U.S. 7,064,211 B2).

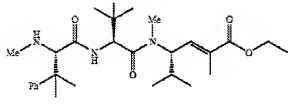
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Kowalczyk et al. teach compounds of formula I;

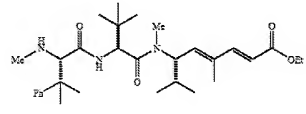


and methods for the use thereof in the treatment of cancer (see abstract, col. 1, lines 65-67, and col. 4-5). Importantly, Kowalczyk et al. teach that the compounds of formula I demonstrate anti-tumor activity and can be made into pharmaceutical compositions or salts thereof for the treatment of various cancers including ovarian cancer (i.e. applicant's elected tumors; see col. 2, lines 20-33, col. 60, lines 30-35 and col. 103, lines 21-50). In particular, the compounds of formula I are taught by Kowalczyk to exhibit growth inhibitory effect on cancer cell lines maintained in vitro or in animal

studies using a scientifically acceptable cancer cell xenograft model; cause tumor regression in vivo; exhibit low sensitivity to MDR and low cytotoxicity and exhibit a favorable therapeutic profile (see col. 99, lines 53-64 and col. 101-102). Certain compounds of formula I according to Kowalczyk exhibit IC50 values less than or equal to 10 μM while others are in the range of 0.1nM-10nM (see col. 100, lines 40-67). Kowalczyk et al. teach compounds that fall within the scope of applicant's formula II such as ER-805590,



and render obvious applicant's compounds delineated in examples 34a and b (see col. 129-130). Similarly, various compounds such as E805711 and ER-806147,



also fall within the scope of formula II and render obvious applicant's invention (see col. 129-130 and col 139-140). Kowalczyk et al. further teach that the compounds of the invention were tested in various cancer cell lines including the paclitaxel-inherent resistant cell lines DLD-1, and HCT-15 thus supporting the notion that such compounds are indeed effective in the treatment of paclitaxel resistant tumors (see col. 434, lines 1-21 and col. 436, lines 1-10).

Kowalczyk et al. do not specifically teach the compound of example 129 (i.e. claim 60) or compounds wherein R5 contains a halogen substituted aryl. Likewise, Kowalczyk et al. does not teach administering such compounds after paclitaxel. Moreover, Kowalczyk et al. do not teach R9 wherein the isopropyl group configuration differs.

Kowalczyk et al. however does teach that the aryl groups can be substituted or unsubstituted (see col. 64, lines 54-55) thereby suggesting that halogen substitution was envisioned in the invention of Kowalczyk et al. Additionally, Kowalczyk et al. teach compound E806147 with unsaturated bonds and the examiner contends that reduction by one alkenyl group is well within the purview of the skilled artisan and would have resulted in a similar compound with similar activity as compared to applicant's compound 129 (see col. 139-140 for addressing the limitation of claim 24). Likewise, it would be well within the purview of the skilled artisan to test both the D & L configuration of R9 in order to determine the most effective configuration in the compounds for treating cancer (instant claims 25 and 27). Moreover, the Examiner contends that compound E806861 of Kowalczyk et al. would also render obvious applicant's example 129 since it is well within the purview of the skilled artisan to extend "Y" in R9 by one carbon chain during the course of routine experimentation and in view of the disclosure of Kowalczyk et al. who teach that aliphatic chain refers to both saturated and unsaturated alkyl chains of 1 to 20 carbon atoms (see col. 63, lines 12-48).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the compounds of Kowalczyk after treatment of paclitaxel in order to avoid tumor resistance. Moreover, one of ordinary skill in the art through routine experimentation would vary the alkyl chain in R9 in order to obtain the most efficient compounds useful for the treatment of cancers including ovarian tumors. Additionally, one of ordinary skill in the art would have found it obvious to utilize the compounds of Kowalczyk for treating or inhibiting growth of tumors since Kowalczyk et al. teach compounds that are useful in the treatment of various cancers. Thus, given the teachings of Kowalczyk et al., one of ordinary skill in the art would have been motivated to utilize the disclosed compounds of Kowalczyk et al. in the treatment of cancer with the reasonable expectation of providing a method that is efficient in treating and reducing tumor growth including ovarian tumors.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

03/10/2009

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617